19. (Twice Amended) A composition comprising the nucleic acid of claim 1, and a pharmaceutically acceptable carrier.

28. (Twice Amended) An isolated nucleic acid molecule comprising a nucleic acid of SEQ ID NO: 1, wherein the nucleic acid hybridizes to a nucleic acid molecule of SEQ ID NO: 1 under stringent conditions, said stringent condition comprising those in which a salt concentration is from about 0.01 M to about 1.0 M sodium ion at a pH from about 7.0 to about 8.3, and in which a temperature is at least about 30°C for probes comprising nucleic acids of 10 to 50 nt or at least about 60°C for probes comprising nucleic acids of more than 50 nt, wherein sequences at least about 85% homologous to each other remain hybridized to each other.

Pursuant to 37 C.F.R. 1.121(c), a marked up version of the claims showing the changes made appears as Appendix C of this Amendment.

REMARKS

Upon entry of the present amendment, claims 1, 2, 4-5, 7-10, 14, 19-21, 28 and 29 will be pending in the application. Applicants thank the Examiner for properly restoring claim 14 to those claims currently under consideration. The Abstract has been amended as requested by the Examiner. Claims 1, 14 and 19 have been amended to more distinctly point out the subject matter being claimed. Support for claim 2 amendments appears in the specification at least, *e.g.*, on page 15, line 31, through page 16, line 7, and on page 16, lines 21-24. Support for claim 5 amendments appears in the specification at least, *e.g.*, on page 3, lines 10-15. Support for claim 28 amendments appears in the specification at least, *e.g.*, on page 17, line 16, through page 18, line 8. No new matter has been added.

Examiner's Position

In the Office Action the Examiner made the following objections:

(1) The Abstract was objected to for allegedly referring to speculative application of the invention.

(2) Claim 2 was objected to for being in improper dependent form for failing to further limit the subject matter of the previous claim.

The abstract and claim 2 have been amended to address the Examiner's concerns. Applicants assert these objections are now moot and should be withdrawn.

In the Office Action the Examiner made the following rejections:

(1) Claims 1-2, 4-5, 7-10, 14, 19-20, 28 and 29 were rejected under 35 U.S.C. §101 as not supported by a specific, substantial and credible utility, and under 35 U.S.C. §112, first paragraph, for failing to teach how to use an invention without proper utility;

(2) Claims 14 and 29 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description;

(3) Claims 1, 3-4, 19-21, and 28 were rejected under 35 U.S.C. §112, second paragraph, for being indefinite; and

(4) Claims 5 and 28-29 were rejected under 35 U.S.C. §102(b), for being anticipated.

Applicants traverse each of these rejections and addresses each individually as follows.

35 U.S.C. § 101 utility rejection is overcome both on its own, and in combination with the 35 U.S.C. § 112, first paragraph, rejection.

Claims 1-2, 4-5, 7-10, 14, 19-20, 28-29 are rejected by this Examiner as lacking utility and as being non-enabled. The rejection is traversed as applied to the claims as pending. In response to the Examiner's position on the Declaration of William LaRochelle under 37 CFR 1.132 ("LaRochelle Declaration"), filed in Applicants' June 28, 2002, response, as being insufficient to overcome this rejection, Applicants also traverse.

The pending claims are generally drawn to FGF-CX polynucleotides, vectors, host cells and methods of making a FGF-CX polypeptide. It was well known in the art at the time of the invention that polypeptides with high sequence homology to the conserved FGF domains regulate FGFR signal transduction complexes, even though family member may have an overall protein homology of as little as 30%. *See*, specification at p. 2, line 8, through p. 3, line 3. It was also well known in the art that FGF members that stimulated growth of fibroblasts had clinical utility in, *e.g.*, treatment of wounds. For instance, U.S. Patent No. 5,804,213, issued September 8, 1998, entitled "Biologically active aqueous gel wound dressing" ("Exhibit 1") claims a wound

dressing including a biologically active substance for treating the wound, wherein the biologically active substance is a growth factor selected from the group consisting of platelet-derived growth factor, fibroblast growth factor, epidermal growth factor, and transforming growth factor. *See*, Exhibit 1, especially claims 1 and 8. Hence, a nexus between the ability of a peptide factor to stimulate fibroblast growth and clinical utility in wound healing was well known in the art at the time of the invention.

The BLAST comparisons in FIGS. 5-8 and the ClustalW disclosed in FIG. 9 clearly demonstrate high sequence homology between the novel FGF-CX polypeptide of the invention and other FGF family members, especially the known Xenopus FGF-20 protein. *See*, *e.g.*, specification on page 10, lines 10-20, FIGS. 5-9. The specification specifically discloses that FGF-CX is used to stimulates fibroblasts (for accelerating healing of burns, wounds, ulcers, etc), megakaryocytes (to increase the number of platelets), hematopoietic cells, immune system cells, and vascular smooth muscle cells. *See,* page 58, lines 11-13. The specification also discloses that FGF-CX can be used as a reagent for stimulating growth of cultured cells. *See*, page 58, lines 16-17. These disclosures and others throughout the specification clearly provide a specific, substantial and credible utility for the novel FGF-CX polypeptide encoded by the elected nucleic acid of the invention.

As further proof that these utilities disclosed in the application as filed are specific, substantial and credible at the time of the invention, Applicants note that results in the LaRochelle Declaration substantiate the above assertions. In particular, the LaRochelle Declaration demonstrates that the FGF-CX protein of SEQ ID NO:2, which is encoded by the claimed nucleic acid, "stimulates fibroblasts" and "can be used as a reagent for stimulating growth of cultured cells." Fibroblast stimulation is useful for "accelerating healing of burns, wounds, ulcers, *etc.*" The results in the LaRochelle Declaration furthermore establish a direct nexus between the encoded polypeptide and a use related to healing injured or damaged tissues. Thus a credible, specific and substantial utility of the nucleic acids of the claimed invention is established because each nucleic acid encodes the protein of SEQ ID NO:2.

According to the Manual of Patent Examination Practice (MPEP) 8th Edition, only one credible assertion of specific utility need be specified for an invention

> Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

MPEP § 2107(II)(B)(1)(ii). Applicants especially note that the MPEP provides that "other evidence of record (*e.g.*, ... affidavits or declarations from experts in the art" are probative where Applicants' original disclosure asserts at least one specific, credible and substantial utility, which is very much the case in the instant application. *Id.* Hence, the Examiner is obligated to treat the LaRochelle Declaration as evidence of record that is probative of clear assertions of utilities.

In reiterate, the nexus between stimulation of fibroblasts and clinically effective wound healing was well known in the art. *See*, U.S. Pat. No. 5,804,213. The specification discloses, and the LaRochelle Declaration affirms, that FGF-CX stimulates fibroblast growth. Hence, Applicants' FGF-CF encoding polynucleotide has at least one disclosed utility that is credible, substantial and specific.

Applicants believe the utility rejections under 35 U.S.C. § 101, either alone or combined with rejections under 35 U.S.C. § 112, first paragraph, are overcome, and respectfully request that they be withdrawn.

35 U.S.C. § 112, first paragraph, rejection is overcome.

Claims 14 and 29 are rejected as lacking enablement. Claim 14 has been amended to recite "encoding said polypeptide of SEQ ID NO:2 is expressed." The Applicants have amended the claim to clarify that it is the encoded polypeptide that is of SEQ ID NO:2. Applicants request that the now moot rejection of claim 14 be withdrawn.

With respect to claim 29, Applicants respectfully note that the Examiner did not state the grounds for rejection. Applicants request that the rejection of claim 29 be withdrawn or further explained.

35 U.S.C. § 112, second paragraph, rejection is overcome.

Claims 1, 3-4, 19-21 and 28 are rejected as being indefinite for various reasons. Applicants traverse the rejection as applied to the claims as amended and address each below.

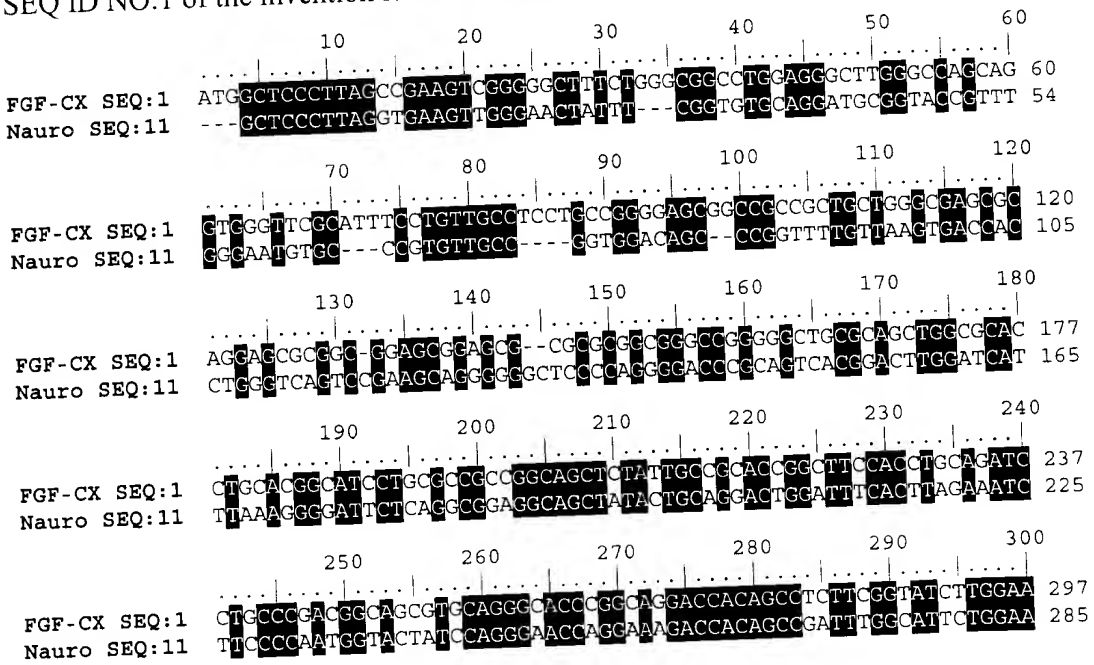
Claims 1 and 28 were rejected for recitation of "FGF-CX." Claim 1 has been amended to remove this reference. However, this reference does not appear in examined claim 28. It was deleted in Applicants response filed June 28, 2002. Applicants believe these rejections are no longer relevant and respectfully request that they be withdrawn.

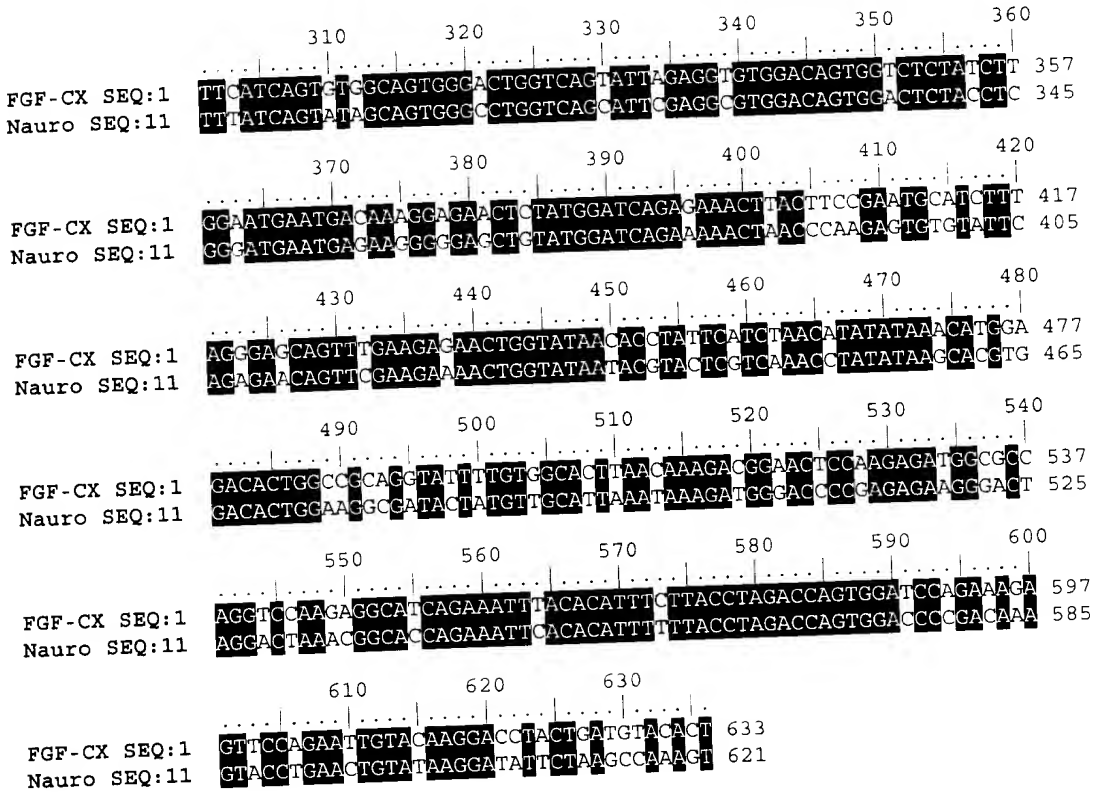
Claims 4 and 28 are rejected for reciting "hybridization ... under stringent conditions." Both claims have been amended to recite the stringent hybridization conditions provided in the specification. Applicants believe these rejections are moot and request that they be withdrawn.

35 U.S.C. § 102(b) rejection is overcome.

Claims 5, 28 and 29 have been rejected as being anticipated by Nauro *et al.* (U.S. Pat. No. 5,512,460) ("Nauro"). Claim 29 depends from claim 28. Applicants traverse the rejection as applied to the claims as amended.

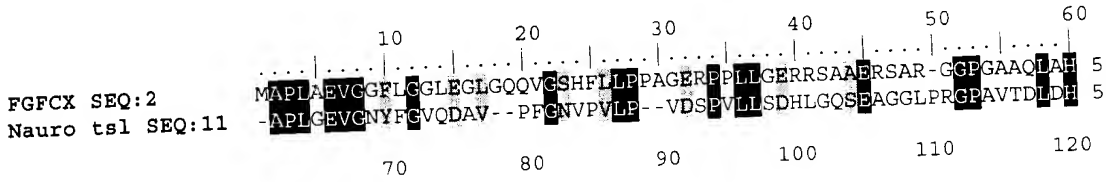
The Examiner reiterates that the Nauro SEQ ID NO:11 cited on page 14 of the December 28, 2001, Office Action ("Paper 12") is prior art. An alignment of the Nauro polynucleotide and SEQ ID NO:1 of the invention is shown below.

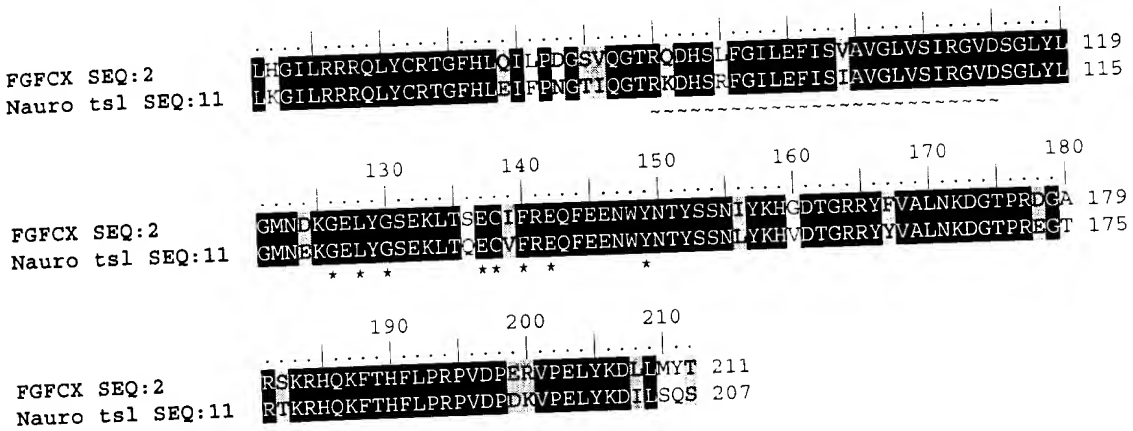




Claim 28 as amended requires that the claimed nucleic acid hybridize to the nucleic acid of SEQ ID NO:1 under stringent conditions, "wherein sequences at least about 85% homologous to each other remain hybridized to each other." In the above alignment, the 633 nt long FGF-CX SEQ ID NO:1 and the 621 nt long Nauro SEQ ID NO:11 are identical at 423 nt positions, for a percent homology of 66.8% and 68.1%, respectively. This percent identity is well below the 85% homology now recited in claim 28 and incorporated into claim 29 through its dependency. Thus, Nauro cannot anticipate claims 28 and 29.

A ClustalW alignment of the polypeptide encoded by Nauro SEQ ID NO:11 and the encoded FGF-CX polypeptide of SEQ ID NO:2 is shown below. The hydrophobic transport region of SEQ ID NO:13 is marked with a tilde ("~") and the conserved amino acid residues of the FGF family motif are marked with asterisks ("*").





Amended claim 5 recites that the "nucleic acid molecule encodes a polypeptide at least 85% identical to the polypeptide comprising the amino acid sequence of SEQ ID NO:2." In the above alignment, the 211 aa long FGF-CX SEQ ID NO:2 and the 207 aa long translated polypeptide of Nauro SEQ ID NO:11 are identical at 145 aa positions, for a percent homology of 68.7% and 70%, respectively. This percent identity is well below the 85% homology now recited in claim 5. Thus claim 5 cannot be anticipated by the amino acid molecule of Nauro *et al.*

Claims 5, 28 and 29 as amended are not anticipated by Nauro *et al.*, and Applicants request that the Examiner withdraw all §102(b) rejections.

CONCLUSION

Applicants submit that the application is in condition for allowance, and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

No fee is believed due at this time. The Commissioner is hereby authorized to charge payment of any filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 15966-557).

Respectfully submitted,

Dated: November 18, 2002

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APPENDIX A: SUBSTITUTE ABSTRACT

ABSTRACT

The present invention provides FGF-CX polypeptides and polynucleotides, and antibodies that immunospecifically bind to FGF-CX or any derivative, variant, mutant, or fragment of the FGF-CX polypeptide, polynucleotide or antibody. The invention additionally provides methods of use for a FGF-CX polypeptide, polynucleotide and antibody.

APPENDIX B: VERSION MARKED TO SHOW CHANGES MADE IN ABSTRACT

In the specification:

Amend the Abstract on page 81 as indicated below. Replace page 81 with substitute page 81 attached as Appendix A.

The present invention provides FGF-CX polypeptides and polynucleotides, and antibodies that immunospecifically bind to FGF-CX or any derivative, variant, mutant, or fragment of the FGF-CX polypeptide, polynucleotide or antibody. The invention additionally provides methods <u>of use for a</u> [in which the] FGF-CX polypeptide, polynucleotide and antibody[are used in detection and treatment of pathological states].

APPENDIX C: VERSION MARKED TO SHOW CHANGES MADE IN CLAIMS

In the claims:

Amend the claims as indicated below.

1. (Twice Amended) An isolated [FGF-CX] nucleic acid molecule encoding a polypeptide comprising a sequence of SEQ ID NO:2, or the complement of said nucleic acid molecule.

2. (Amended) The nucleic acid molecule of claim 1, wherein said nucleotide sequence encodes a polypeptide of SEQ ID NO:2, or the complement of said nucleic acid molecule, said polypeptide having an activity selected from the group consisting of:

a fibroblast growth factor-like activity;

a cell proliferative activity;

a glia activating activity; and

a neuroprotective-like activity.

4. (Amended) The isolated nucleic acid molecule of claim 1, said molecule hybridizing under stringent conditions to a nucleic acid sequence complementary to a nucleic acid molecule comprising the sequence of nucleotides of SEQ ID NO:1, or the complement of said nucleic acid molecule, said stringent condition comprising those in which a salt concentration is from about 0.01 M to about 1.0 M sodium ion at a pH from about 7.0 to about 8.3, and in which a temperature is at least about 30°C for probes comprising nucleic acids of 10 to 50 nt or at least about 60°C for probes comprising nucleic acids of more than 50 nt.

5. (Twice Amended) The isolated nucleic acid molecule of claim 1, said molecule encoding the amino acid sequence of SEQ ID NO:2, said amino acid sequence further comprising one or more conservative amino acid substitutions, wherein said substitutions do not alter the functional ability of the encoded FGF-CX protein, and wherein the nucleic acid

molecule encodes a polypeptide at least 85% identical to the polypeptide comprising the amino acid sequence of SEQ ID NO:2.

14. (Thrice Amended) A method of producing an isolated FGF-CX polypeptide of SEQ ID NO:2, said method comprising the step of culturing the host cell of claim 10 under conditions in which the nucleic acid molecule encoding said polypeptide of SEQ ID NO:2 is expressed.

19. (Twice Amended) A [pharmaceutical] composition comprising the nucleic acid of claim 1, and a pharmaceutically acceptable carrier.

28. (Twice Amended) An isolated nucleic acid molecule comprising a nucleic acid of SEQ ID NO: 1, wherein the nucleic acid hybridizes to a nucleic acid molecule of SEQ ID NO: 1 under stringent conditions, said stringent condition comprising those in which a salt concentration is from about 0.01 M to about 1.0 M sodium ion at a pH from about 7.0 to about 8.3, and in which a temperature is at least about 30°C for probes comprising nucleic acids of 10 to 50 nt or at least about 60°C for probes comprising nucleic acids of more than 50 nt, wherein sequences at least about 85% homologous to each other remain hybridized to each other.